

## Original Article

# Calcium intake and the risk of stroke

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**Abstract:** Objective: Prospective cohort studies have suggested that dietary calcium intake is associated with the risk of stroke; however, the results are inconsistent. We conducted a meta-analysis of published studies to assess the relationship between calcium intake from diet and the risk of stroke. Methods: We searched MEDLINE, EMBASE, and OVID for relevant studies until January 1, 2013. Included for analysis were prospective cohort studies that reported relative risks with 95% confidence intervals (CI) for the association between calcium intake from diet and the stroke risk. Categorical, heterogeneity, publication bias, and subgroup analyses were performed. Results: There were 492,755 participants from ten studies, with 9,329 cases of stroke. For the highest versus lowest category of dietary calcium intake, the relative risk of total stroke was 0.87 (95% CI: 0.73-1.00). The pooled relative risk was 0.80 (95% CI: 0.62-0.98) for ischemic stroke, 0.95 (95% CI: 0.59-1.33) for intracerebral hemorrhage; and 0.96 (95% CI: 0.60-1.33) for subarachnoid hemorrhage. An inverse association between dietary calcium intake and stroke risk was observed in Asian populations (RR 0.68, 95% CI: 0.56-0.80) and participants with < 800 mg/d average dietary calcium intake (RR 0.74, 95% CI: 0.64-0.85). Conclusion: High dietary calcium intake was associated with a reduced risk of stroke, especially in ischemic stroke, Asian populations, and participants with < 800 mg/d average dietary calcium intake.

**Keywords:** Calcium, ischemic stroke, meta-analysis, prospective study

### Introduction

Stroke is a most important cause of disease and disability global. In the United States, approximately 795,000 people have a stroke each year, and 6.4 million Americans are stroke survivors [1]. The need for prevention of stroke is extensively recognized [1]. Weight reduction, increased physical activity, and alcohol control are important for the prevention of stroke [2-4]; however, understanding the role of other lifestyle factors, especially diet and nutrition, may provide additional prevention strategies [5-8]. Calcium is a dietary factor with the potential to influence the risk of stroke through several mechanisms, including influences on blood pressure and insulin resistance [9, 10].

Calcium supplements, with or without vitamin D, have been recommended for the prevention or treatment of osteoporosis [11]. Recently, a meta-analysis of randomized controlled trials performed by Reid *et al.* [12] showed that cal-

cium supplements did not provide a statistically significant increase in the risk of stroke. However, the exact relationship between dietary calcium intake and the risk of stroke remains unclear and controversial. Two prospective studies showed that dietary calcium intake had a significant inverse association with the risk of stroke, [13, 14] but a recent European cohort study showed that increasing dietary calcium intake did not confer significant stroke benefit [15].

We performed a meta-analysis included prospective cohort studies, using strict criteria for inclusion, to evaluate the relationship between calcium intake from diet and the risk of total stroke and various stroke subtypes.

### Subjects and methods

We reviewed the literature and performed a meta-analysis in accordance with the Meta-analysis of Observational Studies guidelines

and the Preferred Reporting Items for Systemic Meta-analysis statement [16-18].

### *Literature search strategy*

A systematic search of MEDLINE (from 1966 to January 1, 2013), EMBASE (from 1980 to January 1, 2013), and OVID (from 1950 to January 1, 2013) was performed using medical subject headings (MeSH) or free text words. The search terms were combined with outcomes (stroke, ischemic stroke, cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebrovascular accident) and the influencing factor (calcium intake, dietary calcium, and total calcium). In addition, we searched the reference lists of relevant primary study articles and reviews, meeting abstracts, and clinical guidelines. We did not contact authors of the primary studies for any additional information.

### *Selection criteria*

Independent reviewers evaluated the selected studies using the inclusion criteria for the study. Consensus was reached for disagreements over inclusion of studies and interpretation of data. The inclusion criteria were as follows: 1) prospective cohort study; 2) adult population; 3) the influencing factor of interest was dietary calcium intake; 4) the outcome was stroke; 5) risk estimates (relative risk [RR] or hazard ratios [HR]) with the 95% confidence interval (CI) for each category of baseline dietary calcium intake and/or for dietary calcium intake as a continuous variable were reported; and 6) follow-up of at least 2 years (mean or median).

### *Data extraction and quality assessment*

Two independent reviewers extracted data by using a standard data collection form. Discrepancies were determined by discussion with another investigator. We extracted the following data: publication year, name of the study, the last name of first author's, country, sex and age range of participants, recruitment time, study period, number of stroke cases, cohort size, method of stroke and calcium intake ascertainment, variables adjusted in the analysis, and risk estimates with corresponding confidence intervals.

We also extracted the RRs and 95% CIs that reflected the greatest degree of control for

potential confounders for use in the main analyses. Studies that did not meet the required criteria during the initial review were excluded from the study. Instead of providing aggregate scores, we assessed the quality of individual studies by reporting the key components of study designs, [16, 19] including characteristics of study populations, assessments of exposure and outcome, period of follow-up, and statistical control for potential confounding factors.

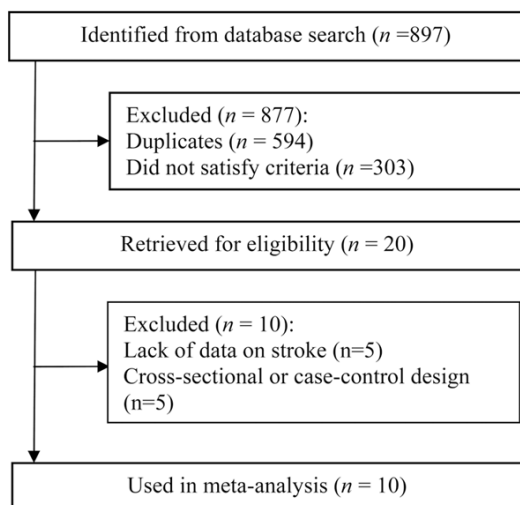
### *Statistical analyses*

We used RR to measure the association in the studies, with the HR also considered as the RR [20]. To summarize the relationship between calcium intake from diet and the risk of total stroke and stroke subtypes, the effect measures were pooled for the highest versus lowest categories for calcium intake from diet. We used the random-effects model for all analyses [21] and Cochran's Q test and  $I^2$  index to assess heterogeneity between the selected studies [22]. As in Higgins *et al.*, [23]  $I^2$  values of 25%, 50%, and 75% were considered low, moderate, and high, respectively. Funnel plot asymmetry was used to detect publication bias, was measured by Egger's and Begg's tests [24, 25] and the "trim and fill" procedure. The "trim and fill" method assumes that hypothetical "missing" studies exist, inputs their RRs, and recalculates the pooled RR, thus incorporating the hypothetical missing studies [26].

We used subgroup analyses to identify the association between the total stroke risk and the relevant study characteristics (sex, mean age, length of follow-up, and number of cohorts) as possible sources of heterogeneity. Stata 10 (StataCorp, College Station, Texas, USA) was used for all the analyses.

## **Results**

**Figure 1** outlines the steps in our literature search. There were 897 articles identified from database search. After evaluations of titles and abstracts, we excluded 877 studies, 594 of which were duplicates in three databases, while another 303 did not satisfy criteria due to animal studies, other publication types or did not relate to the exposure or outcome. After evaluating titles and abstracts, we identified 20 articles that met the inclusion criteria. Several articles were excluded because of a lack of



**Figure 1.** Flowchart for study selection.

essential data. Ten studies met the inclusion criteria for the final meta-analysis [13-15, 27-33]. The reviewers reached good agreement on the inclusion of studies (Cohen's unweighted  $\kappa = 0.90$ ).

*Study characteristics*

**Table 1** lists the included studies. Our analysis included 492,755 participants from ten studies with 9,329 strokes. The selected cohort studies were from seven different countries (Two from the United States, [13, 31] two from Japan, [14, 32] one from the United States including Japanese participants [30], and one each from Finland, [29] Netherlands, [27] Sweden, [28] German, [15] and China [33]). Five studies recruited both male and female participants, [14, 15, 27, 32, 33] whereas three recruited only males [13, 29, 30] and two recruited only females [28, 31]. The age of the participants included was  $\geq 34$  years. The length of the studies ranged from 8 to 22 years (median, 11 years), and most of studies used food-frequency questionnaires for dietary assessment. The median intake of calcium was 1,145 mg/day for the highest categories and 395 mg/day for the lowest categories. The most frequent confounders we adjusted for included physical activity, smoking status, age, body mass index (BMI), hypertension/blood pressure, and alcohol consumption. The total energy intake was adjusted for in six studies, [15, 27-30, 32] and other dietary intakes were adjusted for in five studies [14, 15, 27, 28, 32].

*Main analysis*

Ten prospective cohort studies [13-15, 27-33] with 492,755 participants and 9,329 stroke cases were included in this analysis. In the meta-analysis, a statistically significant inverse relationship was found between higher calcium intake from diet and the total stroke risk such that total stroke risk was 13% lower among the individuals with the highest intake of calcium from diet than among those with the lowest intake (RR, 0.87; 95% CI, 0.73-1.00) (**Figure 2**). There was moderate heterogeneity across studies ( $P < 0.01$ ;  $I^2 = 64.8\%$ ). Sensitivity analysis showed that the study conducted by Larsson *et al.* [29] contribute most to that heterogeneity and the exclusion of this led to a pooled estimate of RR of 0.82 (95% CI, 0.71-0.94). After exclusion of this cohort, there was low study heterogeneity ( $P = 0.10$ ;  $I^2 = 37.3\%$ ).

Five studies provided results for stroke subtypes, [14, 28, 29, 31, 32] and two studies reported only results for ischemic stroke [13, 33]. For these seven studies, the combined RRs for the highest versus lowest categories of calcium intake from diet were 0.80 (95% CI, 0.62-0.98) for ischemic stroke, 0.95 (95% CI, 0.59-1.33) for intracerebral hemorrhage, and 0.96 (95% CI, 0.60-1.33) for subarachnoid hemorrhage (**Table 2**).

Further stratified analyses show that an inverse association between dietary calcium intake and stroke risk was observed in Asian populations (RR 0.68, 95% CI: 0.56-0.80), while no association was observed in American populations (RR 0.87, 95% CI: 0.70, 1.04) or in European populations (RR 1.07, 95% CI: 0.96, 1.18). Moreover, a statistically significant inverse relation between dietary calcium intake and stroke risk was observed in participants with  $< 800$  mg/d average dietary calcium intake (RR 0.74, 95% CI: 0.64-0.85), and no association was observed in participants with  $\geq 800$  mg/d average dietary calcium intake (RR 1.07, 95% CI: 0.96, 1.73).

*Subgroup analyses*

**Table 2** shows the results of the subgroup analyses stratified by study characteristics. Overall, an inverse relationship between calcium intake from diet and total stroke risk was not substantially modified by age or length of follow-up. We

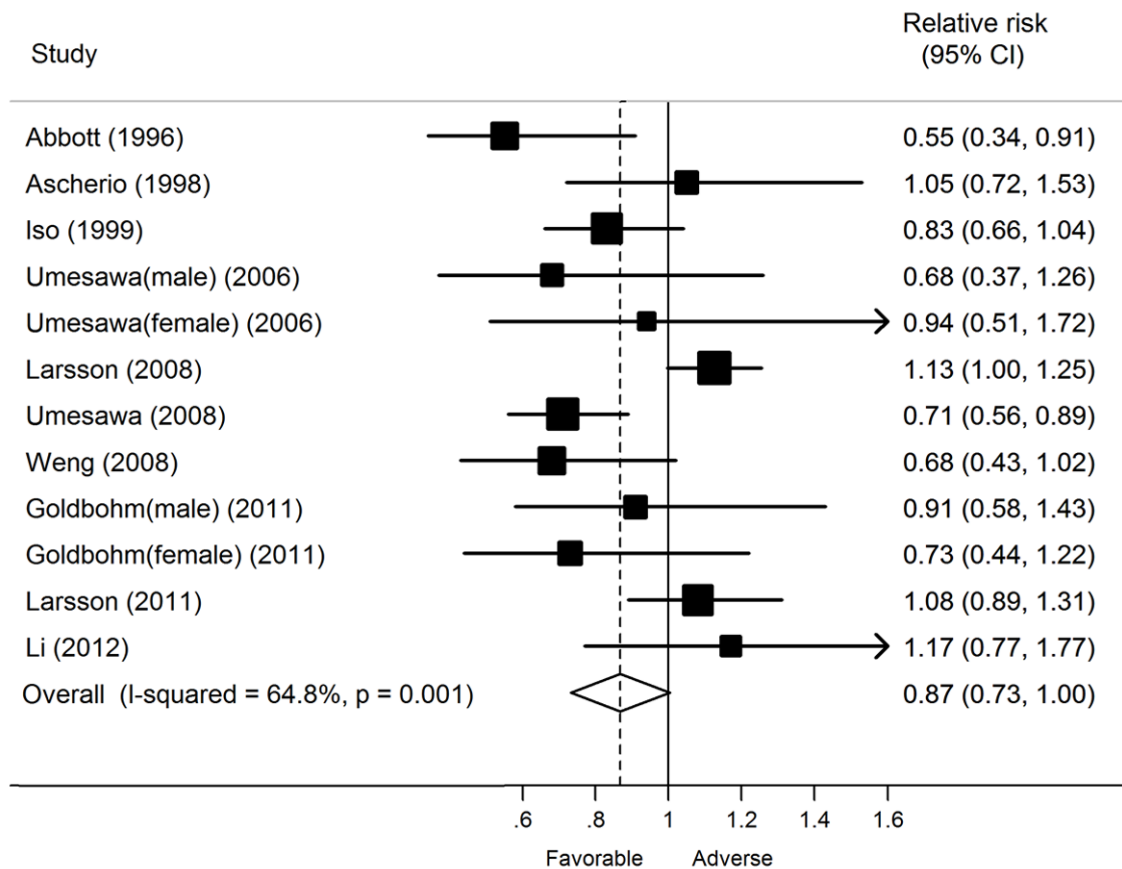
## Calcium and stroke risk

**Table 1.** Characteristics of the prospective studies included in the meta-analysis of published studies on calcium intake and the risk of stroke

Study, cohort study name (country)	Sex/ Age, y	Recruit- ment Time (Years of follow-up)	No of cases (cohort size)	Stroke Ascertainment	Calcium intake Assessment	RR (95% CI) for Highest vs. Low- est Category of Calcium Intake	Adjustments
Ascherio et al, 1998; Health Professionals Follow-up Study (United States)	Male, 40-75	1986 (8)	328 total strokes (43,738)	Medical records or death certificates	Validated FFQ	1.05 (0.72, 1.53)	Age, total energy intake, smoking, alcohol, consumption, history of hypertension, history of hypercholesterolemia, parental history of myocardial infarction before age 65years, profession, and quintiles of BMI, and PA.
Iso et al, 1999; Nurses' Health Study (United States)	Female, 34-59	1980 (14)	690 total strokes, 386 ISs, 74 ICHs, and 129 SHs (85,764)	Medical records	Validated FFQ	0.83 (0.66-1.04)	Age and smoking.
Umesawa et al, 2006; Japan Collaborative Cohort Study (Japan)	Female/ Male, 40-79	1988-1990 (9.6)	566 fatal strokes, 237 fatal ISs, 140 fatal ICHs, and 101 fatal SHs (110,792)	Death certificates	Validated FFQ	Male: 0.68 (0.37-1.26); Female: 0.94 (0.51-1.72)	BMI, history of hypertension, history of diabetes, smoking status, ethanol intake, potassium intake, and total energy.
Larsson et al, 2008; Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Finland)	Male, 50-69	1985 (13.6)	2702 ISs, 383 ICHs, and 196 SHs (26,556)	Medical records	Validated FFQ	IS: 1.10 (0.98-1.26); ICH: 1.20 (0.87-1.64); SH: 1.56 (0.98-2.47)	Age, supplementation group, number of cigarettes smoked daily, BMI, systolic and diastolic BPs, serum total cholesterol, serum high-density lipoprotein cholesterol, histories of diabetes and coronary heart disease, leisure-time PA, and intake of alcohol and total energy.
Umesawa et al, 2008; The Japan Public Health Center-based study (Japan)	Female/ Male, 40-59	1990-1992 (12.9)	1321 total strokes, 664 ISs, 425 ICHs, and 217 SHs (41,526)	Medical records	Validated FFQ	0.71 (0.56-0.89)	Age, sex, BMI, history of diabetes, medication for hypercholesterolemia, menopause, smoking status, ethanol intake, sodium intake, potassium intake, n-3 fatty acid intake, history of hypertension, and public health center.
Weng et al, 2008; CardioVascular Disease risk FACT or Two-township Study (China)	Female/ Male, ≥ 40	1990-1993 (10.6)	132 ISs (1772)	Self-reported, medical records or death certificate	Validated FFQ	0.68 (0.43, 1.02)	Age, sex, hypertension, use of antihypertensive drugs, diabetes mellitus, area, central obesity, alcohol consumption habits, smoking habit, sex-smoking habit interaction, BMI, self-report heart disease, hypercholesterolemia, hypertriglyceridemia, PA, fibrinogen, apolipoprotein B, and plasminogen.
Goldbohm et al, 2011; Netherlands Cohort Study (Netherlands)	Female/ Male, 55-69	1986 (10)	842 fatal strokes (120,852)	Obtained from the Dutch Central Bureau of Genealogy and the Dutch Central Bureau of Statistics	Validated FFQ	Male: 0.91 (0.58, 1.43); Female: 0.73 (0.44, 1.22)	Age, education, cigarette, cigar, and pipe smoking, nonoccupational PA, occupational PA, BMI, multivitamin use, alcohol, energy, energy-adjusted mono-and polyunsaturated fat, and vegetable and fruit intakes.
Larsson et al, 2011; Swedish Mammography Cohort (Sweden)	Female, 49-83	1997 (10.4)	1680 total strokes, 1310 ISs, 154 ICHs, and 79 SHs (34,670)	Obtained from the Swedish Death Registry.	Validated FFQ	1.08 (0.89, 1.31)	Age, smoking status, pack-years of smoking, educational level, BMI, total PA level, history of diabetes, history of hypertension, aspirin use, family history of myocardial infarction, and intakes of total energy, alcohol, protein, cholesterol, total fiber, and folate.
Li et al, 2012; EPIC-Heidelberg study (German)	Male/ Female, 35-64	1994-1998 (11)	260 total strokes (23,980)	Self-reported or medical records	Validated FFQ	1.04 (0.70 to 1.55)	Sex, age at recruitment, educational level, PA, BMI, smoking categories, lifetime alcohol intake, energy-adjusted dietary vitamin D, saturated fatty acid and total protein intake, total energy intake, self-reported diabetes mellitus at recruitment, use of calcium supplements, dairy calcium intake and non-dairy calcium intake.

BMI: Body mass index; BP: Blood pressure; EPIC: European Prospective Investigation into Cancer and Nutrition study; ICH: Intracerebral hemorrhage; IS: Ischemic stroke; SH: Subarachnoid hemorrhage; PA: Physical activity.

## Calcium and stroke risk



**Figure 2.** Adjusted RRs of stroke risk (95% CI) and dietary calcium intake (highest vs. lowest categories using the random-effects model).

examined sex and number of cohorts as possible sources of heterogeneity. The inverse association was more pronounced among the studies that had  $\geq 40,000$  participants (RR, 0.79; 95% CI, 0.68-0.90), and there was no evidence of heterogeneity ( $P = 0.74$ ,  $I^2 = 0\%$ ). However, no association was seen among the studies with  $< 40,000$  participants (RR, 0.92; 95% CI, 0.68-1.16).

### Publication bias

Visual inspection of the funnel plot showed some asymmetry, and the Egger's test suggested that there was borderline evidence of publication bias ( $P = 0.04$ ), but the Begg's test did not ( $P = 0.22$ ). The "trim and fill" method identified no possible missing studies (Figure 3).

### Discussion

From this meta-analysis, we found that calcium intake from diet is inversely associated with the total stroke risk and ischemic stroke risk, but

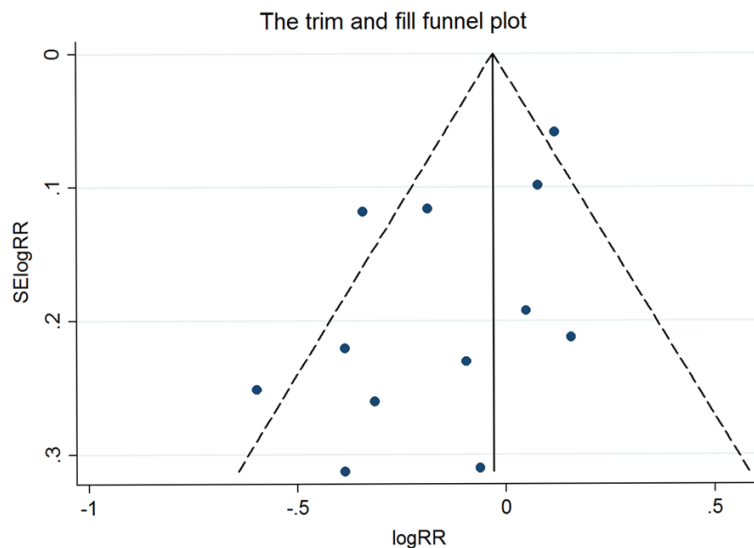
not with hemorrhagic stroke risk. However, fewer cases of hemorrhagic stroke than total and ischemic strokes occurred, which may have reduced the statistical power when assessing the relationship between calcium intake from diet and the risk of hemorrhagic stroke. Moreover, the inverse association between dietary calcium intake and stroke risk was also observed in Asian populations (RR 0.68, 95% CI: 0.56-0.80) and participants with  $< 800$  mg/d average dietary calcium intake (RR 0.74, 95% CI: 0.64-0.85).

The inverse relationship between calcium intake from diet and the risk of stroke appears to be limited to ischemic stroke. Several plausible mechanisms have been proposed for this relationship, including induction of direct and indirect vasodilation, improved endothelial function, benefits on platelet aggregation, and improved insulin homeostasis and lipid metabolism [34-36]. A high-calcium diet can reduce plasma total cholesterol, and an improved high-density lipoprotein to low-density lipopro-

## Calcium and stroke risk

**Table 2.** Stratified analyses of relative risk of stroke according to calcium intake

	No of studies	RR (95% CI)	I <sup>2</sup> (%)	Q Statistic	P Value for Heterogeneity	P Value Between Groups
Overall studies						
Stroke subtypes						
Ischemic stroke	7	0.80 (0.62, 0.98)	70.9	24.07	< 0.01	
Intracerebral hemorrhage stroke	5	0.95 (0.59, 1.33)	51.6	10.33	0.07	
Subarachnoid hemorrhage stroke	5	0.96 (0.60, 1.33)	35.3	7.73	0.17	
Average calcium intake						
< 800 mg/d	6	0.74 (0.64, 0.85)	2.9	6.18	0.40	
≥ 800 mg/d	4	1.07 (0.96, 1.73)	4.1	4.17	0.38	
Populations						
American populations	2	0.87 (0.70, 1.04)	0	0.93	0.34	
European populations	4	1.07 (0.96, 1.18)	6.9	4.30	0.37	
Asian populations	4	0.68 (0.56, 0.80)	0	1.63	0.80	
Subgroup analyses for total stroke						
Gender						
Male	5	0.88 (0.61, 1.15)	74.0	15.37	< 0.01	0.01
Female	4	0.92 (0.75, 1.08)	25.1	4.01	0.26	
Both	3	0.77 (0.56, 0.97)	36.0	3.13	0.21	
Age (years)						
< 60 y	7	0.89 (0.72, 1.06)	21.73	67.8	< 0.01	0.58
≥ 60 y	3	0.83 (0.55, 1.10)	9.21	67.4	0.03	
Length of follow-up (years)						
< 11	5	0.91 (0.78, 1.04)	16.2	7.16	0.31	0.98
≥ 11	5	0.86 (0.83, 0.99)	83.4	24.08	< 0.01	
No. of cohort						
< 40,000	5	0.92 (0.68, 1.16)	78.6	18.66	< 0.01	< 0.01
≥ 40,000	5	0.79 (0.68, 0.90)	0	3.52	0.74	



**Figure 3.** The “trim and fill” funnel plot for meta-analysis of the association between dietary calcium intake and stroke.

tein ratio can improve vasodilation. Animal studies [37, 38] and trials in patients with hypercholesterolemia [39] have shown that calcium intake reduces serum total cholesterol by forming insoluble complexes with fatty acids, thus reducing their absorption. Decreased plasma phosphate and parathyroid hormone may also play a vital role in the vascular effects of increased calcium intake, thus reducing the risk of ischemic stroke [35].

Calcium is particularly abundant in milk and other dairy products. Increased con-

sumption of dairy products protects against ischemic strokes. In a prospective cohort study, Larsson *et al.* [40] showed that increased low-fat dairy consumption is associated with a reduced risk of total stroke (RR, 0.88; 95% CI, 0.80-0.97) and ischemic stroke (RR, 0.87; 95% CI, 0.78-0.98), but not hemorrhagic stroke (RR, 0.96; 95% CI, 0.74-1.25). Elwood *et al.*, in a pooled-analysis of ten cohort studies, demonstrated that the highest quintile of milk consumption is related to a 16% reduction in ischemic stroke risk when compared with the lowest quintile (odds ratio, 0.84; 95% CI, 0.78-0.90). Larsson *et al.* [41] conducted a dose-response meta-analysis to assess the relationship between calcium intake and stroke risk. They determined that calcium intake was inversely associated with risk of stroke in populations with a low to moderate average calcium intake. These results are consistent with our findings.

All of the studies used a prospective cohort design, which enhanced the generalizability of the findings and minimized recall or selection bias. Furthermore, this meta-analysis included a large total population and cohort of stroke patients (492,755 participants and > 9,000 stroke cases), which may significantly increase the statistical power of this analysis.

Possible limitations of this study should be considered. Because our meta-analysis was based on observational studies, we could not exclude the possibility that other factors could explain the observed relationship between calcium intake from diet and stroke risk. Although most study results were adjusted for physical activity, smoking status, age, hypertension, BMI, or blood pressure, and alcohol consumption, the possibility of other confounding factors remains. Only three studies adjusted for supplement intake. It is difficult to exclude the opportunity that specific effects of calcium or other nutrients or other beneficial food components present in the patient's diet were responsible for the observed association. This may have reduced the power of conclusions. Miscalculation of calcium intake from diet might have weakened the power of the relationship because the food-frequency questionnaire was self-administered, and errors could have led to an underestimation of the relative risk estimates. Potential publication bias might

have existed, as shown by the funnel plot and the Egger's test. However, the "trim and fill" analysis identified no possibly missing studies. Finally, because of methodological differences between the individual studies, heterogeneity might have been introduced. After the subgroup analysis, we found that sex and numbers of cohorts were possible sources of heterogeneity and might have reduced the power of conclusions.

In the United States, the Recommended Dietary Allowance of calcium set by the National Institute of Health for men and women aged 51-70 years is 1000 and 1200 mg/d, respectively. The approximate calcium content of some foods is as follows: 138 mg in 1 cup cottage cheese, 415 mg in 8 ounces low fat yogurt, 276 mg in 8 ounces milk, and 73 mg in 1 slice white bread [42]. According to a recent report by WHO, 5.5 million deaths occurred due to stroke in 2008 [43]. Given that the mortality for stroke is 1 in 3, a 13% reduction in the rate of stroke by increasing dietary calcium intake throughout the population could avert nearly 1 million deaths from stroke each year [44].

In summary, in our meta-analysis, we found a significant inverse relationship between dietary calcium intake and the total stroke risk, especially in ischemic stroke, Asian populations, and participants with < 800 mg/d average dietary calcium intake. Furthermore, several well-designed and stratified cohort studies, with adequate control for confounding factors, are needed to gain a better understanding of the underlying biology of the link between dietary calcium intake and stroke risk.

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### Disclosure of conflict of interest

None.

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